Summary

Ruptured sinus of Valsalva aneurysms in six patients have been investigated and then repaired under extracorporeal circulation or hypothermia. The clinical and anatomical features and investigations are described and are compared with cases recorded in the literature. The operative techniques are also described.

The investigation of greatest value in the diagnosis and anatomical location of this lesion is retrograde aortography.

In two of these six cases atrial septal defects were found, an association not previously reported. In three of the patients the presentation was atypical in that it was of gradual onset. One patient died two months after operation.

Four of these patients were under the care of Dr. D. Evan Bedford and Dr. Walter Somerville. We are grateful to them for permission to publish these cases and for their help in writing this report. We are also grateful to Dr. C. B. Matheson, who referred one patient and provided us with follow-up data. We are also grateful to Dr. J. N. Pattinson for carrying out the angiocardiographic investigations.

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GAMMA-GLOBULIN FOR PREVENTION OF RUBELLA IN PREGNANCY

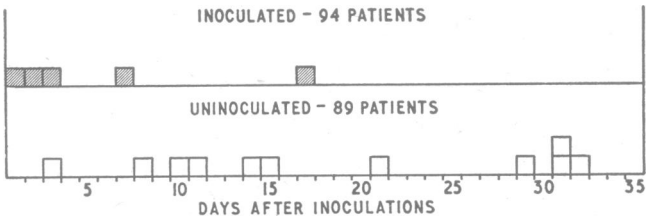
BY

J. C. McDONALD, M.D.
Epidemiological Research Laboratory, Colindale, London

A national survey conducted in Britain by the Ministry of Health and General Register Office (Manson *et al.*, 1960) showed that for women who had rubella in the first 12 weeks of pregnancy in 1950–3, the risk of malformation in live-born infants was 15.8%, compared with 2.3% in controls. The risk of abortion or stillbirth was also higher in the rubella series—9.5% compared with 4.8%. Audiometric examination of a sample of the children at the age of 3–5 years in the survey showed that 30% of those whose mothers had rubella in the first 16 weeks of pregnancy had severe congenital perceptive deafness, though in half these the defect was unilateral (Jackson and Fisch, 1958). Similar estimates for the risk of foetal malformation after maternal rubella have been reported from the United States (Siegel and Greenberg, 1960), Australia (Pitt, 1961), and Sweden (Lundström, 1962); a recent report from New Zealand (Liggins and Phillips, 1963) put it rather higher. Passive immunization is the only means at present available for protecting pregnant women who have been exposed to infection from this considerable hazard.

Lundström *et al.* (1961) summarized the attempts that have been made to assess the prophylactic effect of convalescent serum, convalescent gamma-globulin, and pooled gamma-globulin in rubella. Very few studies have been adequately controlled or large enough to give statistically significant results. Trials in children with normal gamma-globulin by Landon *et al.* (1949) in New York and by Grayston and Watten (1959) in Taiwan provide the best evidence of protection. It is probable that only three batches of gamma-globulin were used in these trials, however, and Korns (1952) has shown that results may vary from batch to batch. Convalescent serum and gamma-globulin prepared from convalescent serum have not been shown to be better than normal gamma-globulin, or even as good. There is little evidence that any form of passive immunization will protect adult women from rubella, let alone protect the foetus.

In England and Wales gamma-globulin prepared by the Blood Products Laboratory of the Lister Institute from the pooled plasma of normal adult donors by the method of Kekwick and Mackay (1954) is distributed to doctors by public health laboratories. Gamma-globulin was made available in 1954 for women exposed to rubella in early pregnancy. Since 1961 the British product has been supplemented from France and Holland. Several attempts were made in 1954 and 1955 to arrange controlled trials in children and in adults, but in only one was the subsequent attack rate high enough to allow any conclusion to be drawn. This trial was in five wards at the Fountain Hospital, London, in November, 1954, where the patients were exposed to infection. Ninety-four children, selected at random from 183 who had no past history of rubella, were each given 250 mg. of gamma-globulin from 46 different batches. The distribution of the 16 cases that subsequently occurred (see Chart) suggests that the globulin



Cases of rubella in patients given gamma-globulin and in uninoculated controls.

gave protection. Excluding patients with illnesses that began within three days of inoculation, only 2 out of 91 (2.2%) were attacked compared with 10 out of 88 (11.4%) controls (difference ÷ standard error = 9.2 ÷ 3.7 = 2.5).

The ethical and practical difficulty of arranging a properly controlled trial of gamma-globulin for rubella prophylaxis in pregnant women is almost insuperable. For want of better evidence, an attempt has therefore been made in this paper to see what conclusions can be drawn from an analysis of the results reported by doctors in practice who have used gamma-globulin for the protection of their patients. As these patients were subjected to very

varied risks of infection no accurate estimate can be made of the number of cases of rubella that would have occurred had they not been given gamma-globulin. In most infectious illnesses, however, if allowance is made for age, sex, and past history of the disease, the attack rates in persons exposed to a case in the same family tend to be fairly stable. Pregnant women, selected by doctors for gamma-globulin treatment, possibly differ from other women in their susceptibility to rubella ; nevertheless, it may be useful to compare their experience with the attack rates in a series of untreated family contacts. An investigation into the natural infectivity of rubella in families made by the College of General Practitioners (1963) has provided the figures needed for this comparison. A further indication of the effect of gamma-globulin is given by the results obtained with different doses. Once again the possible effects of bias due to selection must be borne in mind.

Materials and Methods

From 1954 until June, 1958, the dose supplied to doctors for the prevention of rubella in adult women was 750 mg. ; it was then increased to 1,500 mg., but reduced again to 750 mg. from June to September, 1961, because of shortage. During 1961 some gamma-globulin imported from France was used in similar dosage to supplement that prepared at the Lister Institute. Each doctor was asked to complete a brief report form giving information on the age of the patient, the nature of the contact, the dose given, and the result up to 28 days after inoculation. From 1954 to the end of 1961 16,121 doses were issued, and by the end of March, 1962, forms had been returned for 14,054 (87%), of which 12,927 related to the use of Lister Institute gamma-globulin. The remaining 1,127 reports were for French gamma-globulin and are not included in the results given below. Failure to obtain reports from 13% of doctors may possibly have inflated the attack rates very slightly ; cases of rubella tended to be reported quickly whereas records returned after a reminder were usually negative.

During the years in question it was the policy for gamma-globulin to be issued for the prevention of rubella only for women who had had a definite close exposure to infection in early pregnancy. There were no hard-and-fast rules in the matter, but priority was always given to women not known to have had rubella, who were in contact during the first 12 weeks of pregnancy with a case in the same household. A 10% random sample of the records were studied to see at what stage in pregnancy gamma-globulin was given. The required information was given in 1,103 records and in these the distribution was as follows: in first 6 weeks 13%, in 7–10 weeks 33%, in 11–14 weeks 31%, and in 15 weeks or later 23%.

Thus, allowing for an incubation period of about two weeks, less than half the injections were given in time to prevent women from developing rubella during the first trimester of pregnancy, and most of this was given towards the end of the period rather than at the time of greatest risk of severe damage to the foetus.

Results

Of the 12,927 given gamma-globulin, 96 were reported to have developed rubella within 28 days of exposure. Of these 96 cases, 27 occurred within four days of the injection, which may therefore have been given too late to influence the outcome. Attack rates in relation to dose and type of contact are shown in Table I. The rate after contact in the family (1.27%) was substantially higher than after contact elsewhere (0.26%). In the College of General Practitioners (1963) study the rate for untreated women aged 17–44 years after a family exposure was 3.7%, or

TABLE I.—*Rubella Attack Rates (%) in Relation to Dose of Gamma-Globulin and Type of Contact*

	Dose	Type of Contact			
		In Family	Outside Family	Not Known	All Types
No. of women given gamma-globulin	750 mg.	2,700	2,669	53	5,422
	1,500 mg.	3,278	3,709	43	7,030
	Other or N.K.	248	223	4	475
	All doses	6,226	6,601	100	12,927
All cases within 28 days of exposure	750 mg.	40 (*1·48*)	9 (*0·34*)	0	49 (*0·90*)
	1,500 mg.	37 (*1·13*)	8 (*0·22*)	0	45 (*0·64*)
	Other or N.K.	2 (*0·81*)	0 (—)	0	2 (*0·42*)
	All doses	79 (*1·27*)	17 (*0·26*)	0	96 (*0·74*)
Cases within 28 days of exposure excluding those within 4 days of injection	750 mg.	31 (*1·15*)	4 (*0·15*)	0	35 (*0·64*)
	1,500 mg.	25 (*0·76*)	7 (*0·19*)	0	32 (*0·45*)
	Other or N.K.	2 (*0·81*)	0 (—)	0	2 (*0·42*)
	All doses	58 (*0·93*)	11 (*0·17*)	0	69 (*0·53*)

5.5% if those with a past history of rubella were excluded. The difference between 3.7% (17/461) and 1.27% (79/6,226) is most unlikely to be due to chance, though the comparability of the groups remains open to question. Rather better results were obtained with 1,500 mg. than with 750 mg. in both home and other contacts. The records from all types of contact show that the attack rate with 750 mg. (0.90%) was 40% higher than with 1,500 mg. (0.64%), but the statistical significance of this difference was low ($\chi^2=2.5$; $P=0.1$). Exclusion of cases occurring within four days of inoculation did not make the difference any more definite.

Timing of Injection.—Contrary to what might have been expected, the attack rate in home contacts was higher when gamma-globulin was given soon after exposure than when the injection was delayed (Table II). The difference between the rates for all doses given in the first four days after exposure or on the fifth day and later, 1.65% and 0.75% respectively, cannot easily be explained by chance ($\chi^2=6.14$; $P=0.01$), but it is difficult to exclude selective factors that may have contributed to the findings. For example, there might have been a tendency to treat more urgently women who were certain that they had never had rubella than those who were less sure. Delay would also exclude the small proportion of cases of rubella that occur shortly after the first case in the family, which presumably

TABLE II.—*Rubella Attack Rates in Relation to Time Between Exposure and Injection—Home Contacts Only*

Days between Exposure and Injection	750 mg.		1,500 mg.		Other Dose or Dose not Known		All Doses	
	At Risk	Attacked (%)	At Risk	Attacked (%)	At Risk	Attacked (%)	At Risk	Attacked (%)
0–4	1,729	35 (*2·02*)	2,116	29 (*1·37*)	158	2 (*1·27*)	4,003	66 (*1·65*)
5–8	516	3	623	6	47	0	1,186	9
9–12	125	1 } 4 (*0·56*)	131	0 } 8 (*0·96*)	9	0 } 0	265	1 } 12 (*0·75*)
13–18	69	0	78	2	7	0	154	2
19 or more and not known	261	1	330	0	27	0	618	1
Total	2,700	40 (*1·48*)	3,278	37 (*1·13*)	248	2 (*0·81*)	6,226	79 (*1·27*)

result from an earlier unrecognized exposure. The fact that the difference was more apparent with the smaller dose suggests a more interesting possibility. Failure of rubella virus infection to manifest itself may depend on control of a viraemic phase late in the incubation period. As gamma-globulin is eliminated from the body fairly rapidly the concentration at the operative time may have been inadequate after a very early injection, particularly with the smaller dose.

Batch Variation.—During the period in question Lister Institute gamma-globulin for rubella prophylaxis was taken from some 55 different batches. The number of women injected from any given batch was therefore not large and the expected number of cases of rubella correspondingly small. At the stage when 47 batches had been used the distribution of contacts and cases by batch and by type of exposure was examined statistically by Dr. C. C. Spicer. No significant evidence of heterogeneity was found, and there is no indication, therefore, that batches of gamma-globulin varied in potency.

Discussion

None of the findings presented in this paper shows conclusively that normal gamma-globulin was an effective prophylactic against rubella. The evidence from the considerably lower attack rates in treated than in untreated home contacts, the better protection with a higher dose, and the results of the small controlled hospital trial all point to this conclusion, however. Certainly the attack rates in women given gamma-globulin were so low that it would be difficult to demonstrate that any other agent, such as convalescent gamma-globulin, was more potent.

Even taking the most favourable view of the results, the benefit derived from almost 13,000 injections was small. Without gamma-globulin, instead of 96 cases of rubella, there might have been four times as many, so perhaps 300 cases were prevented. If the stage in pregnancy when the injections were given is taken into account probably fewer than 150, or half the cases prevented, would have occurred during the first 12 weeks of pregnancy. On the basis of the rates reported by Manson *et al.* (1960) the number of live-born infants protected from a severe and clinically obvious defect was thus about 20, but the inclusion of deafness detectable with an audiometer would increase this figure to about 50. In addition, a few foetal deaths may have been prevented. During the same eight years, however, there were at least 100,000 children born in Britain with major congenital malformations.

In assessing the value of gamma-globulin there are three other factors which should also be considered. In the first place, prevention of illness in the mother may not be synonymous with protection of the foetus; secondly, though very few reactions of any consequence have been reported this does not prove that the injections were entirely without risk; and thirdly, it is conceivable that gamma-globulin may protect the mother from infections other than rubella. To answer these questions we are trying to obtain records from practitioners on the outcome of the pregnancies. As many defects, especially those associated with rubella, are not apparent until some time after birth it will be a long inquiry and will be possible only if doctors continue to deal tolerantly with requests for information about their patients.

The effect of doubling the dose from 750 to 1,500 mg. was associated with only a modest 29% reduction in attack rate, but this is not very different from findings reported for measles, against which gamma-globulin is known to be effective (McDonald and Cockburn, 1954). In children aged 1–4 years exposed to measles the effect of increasing the dose from about 240 mg. to about 480 mg. was to reduce the attack rate by 37%. The advantage of using 1,500 mg. instead of 750 mg. for the prevention of rubella is in practice very small. It has been mentioned that perhaps 50 live-born children were protected from some degree of congenital defect by 13,000 injections of gamma-globulin, half of which were at the higher dose. If 750 mg. had been used throughout, the estimated number would have been 47, and if 1,500 mg. had been used throughout it would have been 53. It is also worth emphasizing that most of this return for 13,000 injections resulted from the 20% or so given to women exposed to infection in the home during the first 10 weeks of pregnancy. There certainly seems little to be said for giving gamma-globulin to women unless they are known to have been in definite close contact with infection in the first trimester. A dose of 750 mg. is probably sufficient except for women exposed during the first five or six weeks of pregnancy, when perhaps it might be advisable to give more.

Summary

During 1954–61 16,121 doses of normal gamma-globulin were issued to doctors in England and Wales for the protection of women exposed to rubella in pregnancy. Reports were returned for 14,054 (87%), of which 12,927 related to the use of Lister Institute gamma-globulin.

The attack rate within 28 days of exposure in the home was 1.48% after a dose of 750 mg. and 1.13% after 1,500 mg.; the corresponding rates for other types of contact were 0.34% and 0.22%. For all types of contact the attack rate was 40% higher with the lower dose, but the difference was not statistically significant ($P=0.1$).

The rate for all home contacts, disregarding dose, was 1.27%, which is much less than 3.7%, the lowest comparable figure for untreated women.

This and other evidence presented suggests that normal gamma-globulin is an effective prophylactic against rubella in pregnant women. In relation to the size of the problem, however, the contribution that gamma-globulin has made to the prevention of congenital malformations is small.

I am indebted to general practitioners throughout the country for their reports on the use of gamma-globulin and to Mrs. Judith Munk for much help with the analysis. I wish to thank Dr. Brian H. Kirman for permission to mention the results of the trial at the Fountain Hospital in 1954, and Dr. C. C. Spicer for statistical advice.

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